NTP
National Toxicology Program

Draft NTP Technical Report TR 571 on
Kava Kava Extract

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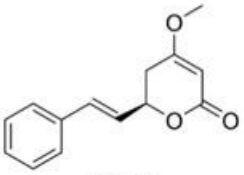
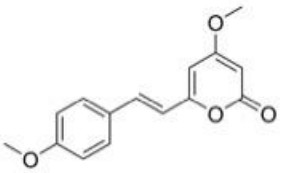
Chemical Structure

Kava Kava extract comprises 30% total kavalactones

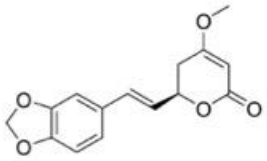
- Consisting of 6 major kavalactones



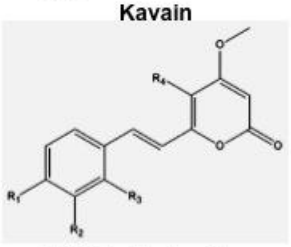
Kavain



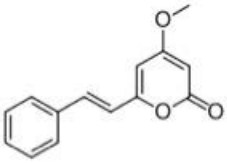
Yangonin



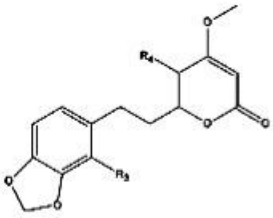
Methysticin



7,8 Dihydrokavain



Desmethoxyyangonin/
5,6 dehydrokavain



Dihydromethysticin

R1,R2,R3,R4 = H

Exposure and Use

- Leading dietary supplement -- crude herb, tinctures, powdered and standardized extract, capsules, tea
- Rapidly growing use in the United States market
- Used for anxiety and nervous disorders (stress, restlessness)
- Promoted as a substitute for Ritalin in children
- Banned in several European countries due to liver effects
- Consumption highly variable -- as high as 2.5 g/day in adults

Nomination

Nominated by National Cancer Institute based on:

- Widespread exposure
- Reports of hepatotoxicity in humans -- cirrhosis, liver failure
- Increasing concern about its use by the U.S. Food and Drug Administration and the World Health Organization
- Lack of toxicity and carcinogenicity data

Experimental Design

Genotoxicity:	In vitro and in vivo (mice)
Two-week studies:	0, 0.125, 0.25, 0.5, 1, 2 g/kg (n = 5)
Three-month studies:	0, 0.125, 0.25, 0.5, 1, 2 g/kg (n = 10)
Two-year studies:	Rats: 0, 0.1, 0.3, 1 g/kg (n = 50) Mice: 0, 0.25, 0.5, 1 g/kg (n = 50)

Two-week Studies

Rats

- No chemical-related effects on survival or body weight
- Minimal hepatocellular hypertrophy in 2 g/kg males and ≥ 0.25 g/kg females
- Increase in liver weight in ≥ 1g/kg males and in ≥ 0.5 g/kg females
- Doses selected for 3-month studies: 0, 0.125, 0.25, 0.5, 1, 2 g/kg

Mice

- No chemical-related effects on survival or body weight
- Increase in liver weight in 2 g/kg group with minimal hypertrophy
- Doses selected for three-month studies: 0, 0.125, 0.25, 0.5, 1, 2 g/kg

Three-month Studies

Rats

- Survival decreased in 2 g/kg males and females
- Significant decrease in body weight in ≥ 1g/kg males and 2g/kg females
- Increase in liver weights of ≥ 0.25 g/kg males and ≥ 0.5 g/kg females
- Increase in hepatocellular hypertrophy in 2 g/kg females
- Clinical pathology findings considered unremarkable
- No effects in sperm parameters of males or the estrous cyclicity of females
- Doses selected for two-year studies: 0, 0.1, 0.3, 1 g/kg
  - No decrease in survival or dose-limiting pathology observed at 1 g/kg
  - Minimal hepatocellular hypertrophy not considered dose-limiting

Three-month Studies

Mice

- Survival decreased in 2 g/kg males and females
- Increase in liver weights in 2 g/kg males and ≥1 g/kg females
- Increase in centrilobular hypertrophy in ≥ 0.5 g/kg males and ≥ 1 g/kg females
- Clinical pathology findings were considered unremarkable
- No effects in sperm parameters of males or the estrous cyclicity of females
- Doses selected for two-year studies: 0, 0.25, 0.5, 1 g/kg
  - No decrease in survival or dose-limiting pathology observed at 1 g/kg
  - Minimal hepatocellular hypertrophy not considered dose-limiting

Two-year Studies

Rats

- Survival
  - Survival of dosed groups of males and females was similar to controls

- Body Weight
  - Decrease in mean body weights of males and females (~ 16%) in 1 g/kg group compared to controls

Neoplastic Lesions - Rats

Neoplasms and Nonneoplastic Lesions of the Testis in Male Rats

	Control	0.1 g/kg	0.3 g/kg	1.0 g/kg
No. Examined	49	50	50	50
Interstitial Cell Hyperplasia	17(1.9)	15 (2.1)	10 (2.4)	4**(2.5)
Bilateral Interstitial Cell Adenoma	29	32	40*	43**
Interstitial Cell Adenoma (includes Bilateral)	37/49 (76%)	44/50 (88%)	49/50 (98%)	46/50 (92%)
Poly-3 test	P = 0.003	P = 0.056	P = 0.002	P <0.001

Historical incidence:
•Two-year gavage studies with corn oil vehicle control groups (mean ± standard deviation): 176/199 (88.4% ± 8.6%), range 76%-94%
• All routes: 1,053/1,298 (81.1% ± 13.4%), range 54%-98%

Nonneoplastic Lesions - Rats

Males and females (high-dose group)

- Liver (hypertrophy, fatty change, cystic degeneration)
- Forestomach (inflammation, ulcer, epithelial hyperplasia)
- Kidney (nephropathy, epithelial hyperplasia)
- Eye (retinal degeneration)
- Pancreas (acinus hepatocyte metaplasia)

Two-year Studies

Mice

- Survival
  - Survival of dosed groups of males and females was similar to controls

- Body Weight
  - Decrease in mean body weights of females (~ 18%) in 1 g/kg group compared to controls

Neoplastic and Nonneoplastic Lesions in Liver of Male Mice

	Control	0.25 g/kg	0.5 g/kg	1.0 g/kg
No. Examined Microscopically	50	50	50	50
Centrilobular Hypertrophy	0	34** (1.0)	30**(2.0)	39**(2.0)
Eosinophilic Foci	28	32	42**	43**
Angiectasis	3 (1.0)	6 (1.0)	7 (1.1)	10* (1.7)
Necrosis	3 (1.7)	10* (2.0)	7 (2.0)	13** (2.0)
Hepatocellular Adenoma	27	32	29	35
Hepatocellular Carcinoma	20	18	26	20
Hepatoblastoma	0/50	4/50 (8%)	9/50 (18%)	12/50 (34%)
Poly-3 test	P < 0.001	P = 0.057	P = 0.002	P < 0.001
Hepatocellular Carcinoma or Hepatoblastoma	20/50 (40%)	21/50 (42%)	30/50 (60%)	25/50 (50%)
Poly-3 test	P = 0.136	P = 0.426	P = 0.046	P = 0.205

Neoplastic and Nonneoplastic Lesions in Liver of Female Mice

	Control	0.25 g/kg	0.5 g/kg	1.0 g/kg
No. Examined Microscopically	50	50	50	50
Centrilobular Hypertrophy	0	20** (1.0)	48** (1.9)	49** (2.0)
Eosinophilic Focus	9	7	16	26**
Hepatocellular Adenoma	8	11	14	5
Hepatocellular Carcinoma	3/50 (6%)	13/50 (26%)	8/50 (16%)	8/50 (16%)
Poly-3 test	P = 0.337	P = 0.007	P = 0.126	P = 0.109
Hepatocellular Adenoma or Carcinoma	10/50 (20%)	21/50 (42%)	20/50 (40%)	13/50 (26%)
Poly-3 test	P = 0.542	P = 0.015	P = 0.036	P = 0.338

Genetic Toxicology Studies

- Bacterial assays (*Salmonella* and *E. Coli*) negative
- No increase in micronucleated erythrocytes in male or female mice after 3-month exposure

Conclusions

- Equivocal evidence of carcinogenic activity in male F344/N rats
  - Marginal increase in testicular adenomas
- No evidence of carcinogenic activity in female F344/N rats
- Clear evidence of carcinogenic activity in male B6C3F1 mice
  - Increased incidence of hepatoblastoma and hepatoblastoma and carcinoma (combined)
- Some evidence of carcinogenic activity in female B6C3F1 mice
  - Increased incidence of adenoma and carcinoma (combined)
- Increases in nonneoplastic lesions
  - Male and female rats and mice: liver
  - Male and female rats and female mice: forestomach
  - Male and female rats: kidney, eye, pancreas